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CAUSEL: an epigenome- and genome-editing pipeline for establishing function of noncoding GWAS variants. - DTU Orbit (08/11/2017)

CAUSEL: an epigenome- and genome-editing pipeline for establishing function of noncoding GWAS variants.
The vast majority of disease-associated single-nucleotide polymorphisms (SNPs) mapped by genome-wide association studies (GWASs) are located in the non-protein-coding genome, but establishing the functional and mechanistic roles of these sequence variants has proven challenging. Here we describe a general pipeline in which candidate functional SNPs are first evaluated by fine mapping, epigenomic profiling, and epigenome editing, and then interrogated for causal function by using genome editing to create isogenic cell lines followed by phenotypic characterization. To validate this approach, we analyzed the 6q22.1 prostate cancer risk locus and identified rs339331 as the top-scoring SNP. Epigenome editing confirmed that the rs339331 region possessed regulatory potential. By using transcription activator-like effector nuclease (TALEN)-mediated genome editing, we created a panel of isogenic 22Rv1 prostate cancer cell lines representing all three genotypes (TT, TC, CC) at rs339331. Introduction of the 'T' risk allele increased transcription of the regulatory factor 6 (*RFX6*) gene, increased homeobox B13 (HOXB13) binding at the rs339331 region, and increased deposition of the enhancer-associated H3K4me2 histone mark at the rs339331 region compared to lines homozygous for the 'C' protective allele. The cell lines also differed in cellular morphology and adhesion, and pathway analysis of differentially expressed genes suggested an influence of androgens. In summary, we have developed and validated a widely accessible approach that can be used to establish functional causality for noncoding sequence variants identified by GWASs.

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